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Clinical aspects of the phosphate transporters NaPi-IIa and NaPi-IIb: mutations and disease associations

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Abstract

The Na^+-dependent phosphate transporter NaPi-IIa (SLC34A1) is mostly expressed in kidney whereas NaPi-IIb (SLC34A2) has a wider tissue distribution with prominent expression in lung and small intestine. NaPi-IIa is involved in renal reabsorption of inorganic phosphate (Pi) from urine and patients with biallelic inactivating mutations in SLC34A1 develop hypophosphatemia, hypercalcemia, hypercalciuria and nephrocalcinosis and –lithiasis in early childhood. Monoallelic mutations are frequent in the general population and may impact on the risk to develop kidney stones in adulthood. SNPs in close vicinity to the SLC34A1 locus associate with the risk to develop CKD. NaPi-IIb mediates high-affinity transport of Pi from the diet and appears to be mostly important during low Pi availability. Biallelic inactivating SLC34A2 mutations are found in patients with pulmonary alveolar microlithiasis, a lung disease characterized by the deposition of microcrystals. In contrast, no evidence for disturbed systemic Pi homeostasis has been reported in these patients to date. Nevertheless, NaPi-IIb mediated intestinal Pi absorption may be a target for pharmaceutical interventions in patients with chronic kidney disease and Pi overload.

Introduction

Phosphate is critical for life. It is required for the synthesis of membrane lipids, DNA and RNA molecules, it forms part of energy rich molecules such as ATP or GTP, it is involved in phosphorylation/dephosphorylation reactions regulating protein activity, and it is a component of apatite giving stability to bone.

In the 21st century, we live in an environment of dietary phosphate excess; however, meeting phosphate needs was not always simple and human beings, along with most organisms, evolved mechanisms to ensure adequate absorption of phosphate from their environment. Being a multi-cellular, multi-organ organism, these mechanisms had to meet both total body homeostasis as well as unitary cellular needs. Renal NaPi-IIa and intestinal Napi-IIb, the first two members of the SLC34 family of sodium dependent phosphate cotransporters discovered, are critical for maintaining total body phosphate homeostasis, NaPi-IIa through regulation of renal excretion and NaPi-IIb through contribution to gastrointestinal absorption. They are both responsible for initiating the transepithelial transport of phosphate, with lesser primary roles in the maintenance of cellular phosphate requirements. However, the function of these two transporters ultimately has an impact on cellular phosphate availability and metabolism and of course on skeletal development and maintenance. The impact of these two transporters on human physiology is revealed when their function is disrupted as reviewed here. The normal physiology of NaPi-IIa and NaPi-IIb will be briefly reviewed followed by a discussion of primary and secondary disorders affecting these transporters.

NaPi-IIa (SLC34A1)

Normal physiology

NaPi-IIa is an electrogenic sodium dependent phosphate transporter mediating the cotransport of 3 Na^+ with one $H_2PO_4^-$ per transport cycle [25]. It is expressed almost exclusively in the apical membrane of the proximal renal tubule where it is responsible for the regulated reabsorption of filtered phosphate. This function is shared with at least

two other sodium dependent phosphate transporters, NaPi-IIc (SLC34A3) and Pit2 (SLC20A2) [4,96]. It has been estimated based on a *Slc34a1* KO mouse model that NaPi-IIa mediates about 70 % of the reabsorption of phosphate from the ultrafiltrate [2]. Prior studies had suggested expression also in osteoblasts [101], osteoclasts [50], and odontoblasts [64]; however, the expression in osteoclasts appears to be very low and of little physiological relevance [1] and overall these studies performed in rodents have not been replicated in humans.

In rodents, NaPi-IIa protein appears later in renal development than NaPi-IIc and continues to increase in expression through the first few weeks of life. NaPi-IIc expression is highest in newborn animals and declines progressively through aging. Thus, it is thought that NaPi-IIa is the major renal phosphate transporter in adulthood. Whether this is also true for humans has remained unknown but recent evidence from genetics may suggest otherwise as discussed below.

The ontogeny of human NaPi-IIa appearance has not been determined; however, studies in premature babies suggest suboptimal renal tubular phosphorus reabsorption in very premature infants, 25 weeks or less, but relatively intact renal phosphorus handling in older premature infants. Overall the findings suggest that tubular phosphorus handling matures during the third trimester, implying that this is the time when the transporters appear, including NaPi-IIa.

Other than age, NaPi-IIa expression is regulated primarily by dietary phosphate intake and the hormones parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) [41]. Low dietary phosphate or malabsorption syndromes resulting in poor phosphate gastrointestinal uptake increase NaPi-IIa expression while high dietary phosphate downregulates NaPi-IIa expression [5]. The major phosphaturic hormones, PTH and FGF23, both downregulate the apical membrane expression of NaPi-IIa facilitating the urinary excretion of excessive dietary phosphate intake. PTH secretion is regulated physiologically by ionized calcium concentrations but also affects phosphate handling, while FGF23 secretion is regulated predominantly by serum phosphate through unknown mechanisms. FGF23 downregulation of renal tubular phosphate absorption requires its cofactor, α-klotho [36].

Human disease associated with NaPi-IIa (SLC34A1) mutations

Mutations in SLC34A1 have been associated with various related diseases both in children and adults. Whereas there is increasing evidence for a role of monoallelic SLC34A1 mutations in adult kidney stone disease, findings from many families with biallelic inactivating mutations in SLC34A1 demonstrate a critical role of NaPi-IIa in intrauterine and postnatal renal phosphate handling.

Urinary Pi wasting is part of generalized inherited or acquired syndromes of dysfunction of the proximal tubule (Debre-DeToni-Fanconi syndrome). Here, we will concentrate on disturbances that are primarily caused by mutations in SLC34A1. Mutations in both SLC34A1 and SLC34A3 result in renal phosphate wasting and nephrocalcinosis and –lithiasis, but the clinical pictures differ in that rickets is a major manifestation of SLC34A3 but not SLC34A1 mutations [4].

Genome wide studies (GWAS) have associated *SLC34A1* with serum Pi [48], kidney stones [105,95,72], hypophosphatemia and low PTH [74], PTH levels in general [84], FGF23 levels [83], risk for chronic kidney disease (see also below [55,56,76,68]), and salt-sensitive hypertension [68]. The biology behind these associations is in part well explained (see below) but in some cases remains to be fully established, i.e. for CKD and salt-sensitive hypertension.

Monoallelic *SLC34A1* mutations have been identified in adult patients with kidney stones and reduced bone density [78], whereas biallelic mutations were found in children with either hypophosphatemia and hyperphosphaturia [81], or with infantile idiopathic hypercalciuria [88] or with nephrocalcinosis and kidney stones [7,74,30,19,67,38]. Patients from one large family with a 21-nucleotide insertion in the transporter also showed symptoms of a more generalized proximal tubular dysfunction with unusually high calcitriol levels atypical for Fanconi-like syndromes [67,17]. In some cases, associations were present with metabolic acidosis or epilepsy, sensorineural deafness and learning deficiencies which may not be directly linked to mutations in *SLC34A1* [23]. Large deletions encompassing *SLC34A1* are found in patients with Sotos syndrome with learning deficiencies, facial dysmorphia, overgrowth, hypercalcemia, and nephrocalcinosis [47].

In pediatric patients, *SLC34A1* mutations are mostly homozygous or compound heterozygous with clinical symptoms showing an autosomal recessive inheritance. Thirty mutated sites have been identified in *SLC34A1*, mostly causing missense mutations, small in-frame deletions, frame shifts or early stop-codons [74,7,19,30,67,78,81,79,17,38,57]. Many of these mutations are located within the predicted highly conserved transmembrane domains of the transporter possibly disturbing folding and/or stability of the protein in the membrane. Consistently, the functional analysis of several of these mutants demonstrated function possibly due to trafficking defects with intracellular retention of the mutant protein [88,81,19,17,23].

An in-frame deletion of 7 amino acids at the cytoplasmic N-terminal tail (91del7) is of particular interest. The mutation has been detected in several patients either in compound heterozygosity or in homozygosity [88,23,38]. The clinical symptoms of homozygous and compound heterozygous patients are similar to patients carrying other *SLC34A1* mutations strongly suggesting that the 91del7 mutation is fully pathogenic. However, functional studies provide evidence for only a very mild transport defect [88,60,23] with only little reduction in apical expression consistent with a possible trafficking defect [88]. Of interest, this mutation has a high minor allele frequency of 0.018 (ExAC http://exac.broadinstitute.org/) suggesting that nearly 2 % of the general population carries this mutation on one allele. Moreover, the combined allele frequency of all pathogenic exonic mutations tested to date is 0.022 and the total allele frequency of all nucleotide changes causing alterations in the amino acid sequence sums even up to 0.07. It is currently unknown why SLC34A1 mutations have accumulated such a high

frequency, whether there has been any advantage during evolution associated with such mutations, and what the clinical consequences of such mutations may be. As discussed below, evidence is emerging that monoallelic mutations may be associated with the risk for kidney stones in adulthood.

SLC34A1 and adult stone formers

Prie et al reported two adult patients with stone disease, reduced bone mineral density and monoallelic SLC34A1 mutations [78]. Unfortunately, no further family data were available testing for segregation of the phenotype with the mutations. When NaPi-IIa constructs expressing these mutations were expressed in Xenopus oocytes, the stimulated phosphate uptake was significantly less than with wild type suggesting that these mutations rendered tubular phosphate reabsorption less resulting in nephrolithiasis or decreased bone mass. An in depth analysis of the effect of these mutations on phosphate transport kinetics, affinity, and transporter localization by Virkki et al [97] confirmed the slightly decreased phosphate transport by the NaPi-IIa mutants but did not disclose any differences in affinity, pH dependence, voltage dependence, or transporter turnover. It remained unclear whether the 30% decrease in transport was sufficient to explain the clinical presentation of the two subjects. Similarly, LaPointe and coworkers [60] explored the association between hypophosphatemic, hypercalciuric stone formation and NaPi-IIa mutations further by sequencing the gene in 28 individuals, investigating affected and unaffected family members for gene variations, and expressing the NaPi-IIa constructs in oocytes and opossum (OK) cells. They identified 5 polymorphisms but failed to find a correlation between the presence of a polymorphism and phosphate wasting within families. When expressed in oocytes, phosphate transport was diminished for some but not all of the genetic variants. They concluded that their study did not support a role for altered NaPi-IIa function as causative for stones.

A major problem in these studies is that stone disease and its association with reduced bone density is highly frequent (up to 10 %) in the adult population. Nevertheless, also GWAS clearly support a role of *SLC34A1* in stone disease [74,95,105]. NaPi-IIa forms homodimers [28] witht both subunits functioning independently [54]. One might speculate that monoallelic mutations either impair the trafficking of dimers of wildtype and mutant protein causing a dominant negative effect or that the function of one normal allele may not be enough to adapt renal Pi handling to changing metabolic and dietary demands.

Pathophysiology of nephrolithiasis and -calcinosis

The pathophysiology leading to hypercalciuria and nephrolithiasis and –calcinosis has been examined using the Slc34a1 KO mice [51,2,88]. These experiments together with the clinical symptoms and biochemical changes in patients with SLC34A1 mutations suggest the renal loss of phosphate and the subsequent development of hypophosphatemia reduce FGF23 levels. Low plasma phosphate and low FGF23 stimulate the activity of the CYP27B1 enzyme mediating the final 1-a-hydroxylation of 25-OH vitamin D3 to the active 1,25-(OH)2 vitamin D3 (calcitriol). Also, the activity of the CYP24A1 enzyme inactivating calcitriol is reduced [88]. High calcitriol levels stimulate intestinal phosphate absorption via NaPi-IIb[11] but also intestinal calcium absorption [13]. The inappropriately high calcium absorption leads to hypercalcemia and hypercalciuria. In urine, high calcium triggers precipitations with phosphate and/or oxalate causing nephrocalcinosis or –lithiasis.

A recent study also demonstrated that *Slc34a1* knock out mice showed diminished renal excretion of osteopontin, a protein that binds calcium and reduces calcium crystallization, and that the combination of *Slc34a1* and *osteopontin* deletion magnified the tendency toward renal mineralization [10]. Osteopontin production is stimulated by FGF23, suggesting that the mechanism for the nephrocalcinosis seen in phosphate wasting states may be due to reduced FGF23 production leading to reduced renal excretion of osteopontin and loss of the antagonistic effect on crystal formation.

Fearn et al [23] reported two patients with a clinical picture different from what has been found in most patients. The first patient was heterozygous whereas the second was compound homozygous for SLC34A1 mutations. Both patients had stone disease, the first patient had also deafness, learning difficulties, CKD stage 4 with low calcitriol and high FGF23 levels. The second patient had pronounced nephrocalcinosis with metabolic acidosis, low calcitriol and high FGF23 concentrations. From a clinical standpoint, these cases also presented an interesting paradox. Although primary phosphate wasting syndromes have been associated with low FGF23 and high active vitamin D levels, the two individuals studied in this paper had the opposite. Although the authors hypothesized that the severely ill condition of the subjects accounted for the elevated FGF23 levels through the development of inflammation, another stimulator of FGF23, these cases point out some of the difficulties in the clinical identification of affected individuals, the role of specific SLC34A1 variants in the clinical picture, and the contribution of FGF23 and vitamin D to the disease manifestations.

NaPi-IIa and chronic kidney disease

Genome-wide association studies (GWAS) have identified more than 100 risk loci in the human genome associated with a higher risk for developing chronic kidney disease [56,76,55,68]. Consistently, associations were found for markers next to the gene locus harboring SLC34A1 with significant odds ratios for developing CKD between 1.05 and 1.10 in a cohort of European and mixed Asian, African and European descent, respectively [18]. However, none of these markers resides within the coding region of SLC34A1 and no studies have been undertaken to test the impact of these SNPs on SLC34A1 expression. Thus, the pathophysiological and clinical relevance of these SNPs remains to be elucidated. A recent study linked lower mRNA expression levels of NaPi-IIa in kidney biopsies from patients with CKD to the risk of developing CKD because of low NaPi-IIa abundance [62]. Whether the reduction of NaPI-IIa mRNA is cause or consequence in these patients is unclear and low NaPi-IIa mRNA may simply reflect lower nephron mass or reduced expression due to high FGF23 and PTH levels.

Mutations in hormones and proteins regulating NaPi-IIa

Mutations in the hormones and proteins regulating NaPi-IIa expression and function will also result in clinical disease. These will be discussed briefly. For a more extensive review the reader is referred to several recent reviews [99,100,3].

Hypophosphatemia and renal phosphate wasting due hyperparathroidism can be the result of inactivating mutations in the calcium sensing receptor (CaSR), the G-alpha 11 protein (GNA11), the clathrin adaptor protein AP2 (AP2S1), the tumor suppressor menin (MEN1), the cyclin dependent kinase inhibitor (CDKN1B), parafibromin (CDC73), or activating mutations of the proto-oncogene RET (RET) or the chorion specific transcription factor (GCM2) [70]. Clinically these syndromes are frequently dominated more by the presence of hypercalcemia than by abnormalities in phosphate metabolism. In contrast, several gene mutations associated with rare syndromes of hypoparathyroidism can produce hyperphosphatemia (reviewed in: [14]). The rare syndrome of pseudohypoparathyroidism is also associated with hyperphosphatemia due to renal resistance to the phosphaturic effect of parathyroid hormone [14,90], resulting from mutations in the alpha subunit of the stimulatory G protein $G_{\alpha s}$.

Elevations in FGF23 also cause hypophosphatemia due to downregulation of NaPi-IIa and suppression of calcitriol levels. High FGF23 can be caused by mutations in the protein itself preventing its cleavage (autosomal dominant hypophosphatemic rickets), mutations in PHEX (phosphate regulating gene with homologies to endopeptidases, X-linked hypophosphatemic rickets), Dentin Matrix Protein (DMP1), ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), or FAM20C (Family with sequence similarity 20C), for which inactivating mutations can produce autosomal recessive hypophosphatemic rickets (reviewed in [21]).

Syndromes associated with high FGF23 levels can be distinguished from hyperparathyroid syndromes clinically by the absence of hypercalcemia and the normal or low active 1,25-$(OH)_2$ vitamin D_3 levels. In contrast, genetic conditions leading to low FGF23 levels or function cause hyperphosphatemia. These rare syndromes, all entitled

tumoral calcinosis, encompass inactivating mutations in GALNT3 (UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactos-aminyl transferase-3), an enzyme that O-glycosylates FGF23 and prevents excessive cleavage of the protein; mutations in FGF23 that result in excessive cleavage of FGF23 protein; and inactivating mutations in a-Klotho, leading to the inability of FGF23 to activate its cognate receptors.

PDZ domain proteins play a central role in NaPi-IIa trafficking and localization [31]. Karim and coworkers described three mutations in the protein NHERF1 (Na-H Exchanger Regulatory Factor, Isoform 1) associated with decreased tubular reabsorption of phosphate and low bone mineral and/or nephrolithiasis [43]. These heterozygous mutations resulted in enhanced responsiveness to parathyroid hormone in a cell culture model, leading to lower phosphate transport rates. Urinary cAMP excretion, a marker of PTH effects, was higher in individuals expressing the NHERF1 mutations. However, SNPs in NHERF-1 are frequent in the general population and their relevance for renal phosphate handling are currently unknown.

NaPi-IIb (SLC34A2)

Physiology of NaPi-IIb

NaPi-IIb (SLC34A2) was initially cloned from small intestine [34] where it is expressed at the apical side of enterocytes lining the small intestine. Considerable species differences exist between mice, rats and humans. In mice, NaPi-IIb is mostly expressed in ileum whereas in rats and humans, NaPi-IIb is expressed in duodenum and jejunum but is absent from ileum [27,69,80]. The physiological relevance of this difference is not known. NaPi-IIb is an electrogenic Na^+-phosphate cotransporter coupling the transport of 3 Na^+ to the transfer of one $H_2PO_4^{2-}$. Its transport mechanism has been reviewed in detail elsewhere [25]. The apparent affinities for Na^+ and phosphate are around 25 mM and 10 µM, respectively [25]. The high affinity for phosphate may suggest that the cotransporter is easily saturated at normal intestinal phosphate concentrations and may be more important during times of low phosphate availability.

NaPi-IIb is found in several organs outside of the small intestine including testis, mammary glands, salivary glands, and lung. While the role in testis has not been examined, NaPi-IIb is involved in mediating secretion of phosphate into milk and saliva, respectively [35,73]. In lung, NaPi-IIb is expressed in type II alveolar cells and may play a role in controlling phosphate levels in the intraalveolar fluid [93,86].

Regulated expression and activity of NaPi-IIb has been best examined for the small intestine. There, NaPi-IIb is regulated by dietary phosphate intake. While high phosphate intake downregulates NaPi-IIb protein abundance, low phosphate availability stimulates NaPi-IIb expression [80]. Also, 1,25-$(OH)_2$ vitamin D_3 stimulates NaPi-IIb expression through the Vitamin D receptor (VDR). Nevertheless, the adaption of NaPi-IIb to dietary phisphate intake does neither require 1,25-$(OH)_2$ vitamin D_3 nor the VDR [11]. Also estrogens stimulate NaPi-IIb expression [104] whereas epidermal growth factor (EGF) appears to reduce expression [103].

For a more detailed review on the regulation of NaPi-IIb in the intestine the reader is referred to a recent review [33].

Human disease associated with NaPi-IIb (SLC34A2) mutations

Homozygous and compound heterozygous mutations in *SLC34A2* have been detected in patients with pulmonary alveolar microlithiasis (PAM), a disease characterized by progressive deposition of calcium phosphate containing microcrystals in lung, inflammation, tissue destruction, pulmonary fibrosis and insufficiency, and cor pulmonale in some patients [15,24,37]. In a few patients, heterozygous mutations were linked to testicular microlithiasis but this has not been replicated by independent studies [15]. At present, 20 distinct mutations have been reported, including deletions, frame shifts, missense mutations as well as changes in potential splice sites and in the promoter region [15,98,37,40,89,42,102,106,20,66,75,39].

The impact of these mutations on transport activity, trafficking or protein stability has not been well characterized. One study provided evidence that at least two truncated mutants do not transport Pi upon expression in Xenopus oocytes [37].

NaPi-IIb is expressed in lung in type II pneumocytes [93], cells important for surfactant production. The capacity of one *SLC34A2* mutant to transport Pi after expression in an alveolar cell line was diminished suggesting that NaPi-IIb could play a role in controlling extracellular Pi levels in alveolar fluid [65].

Despite the prominent expression of NaPi-IIb in intestine, no phenotype related to intestinal Pi absorption or systemic Pi homeostasis is known in patients with *SLC34A2* mutations. Several mouse models of *Slc34a2* deletion have been generated, mostly to characterize the role of NaPi-IIb in intestine [32,85]. These models demonstrate that NaPi-IIb is the main cotransporter in the ileum, but its absence has only mild consequences on Pi and hormonal levels [53,32,85]. In contrast, a lung epithelium specific NaPi-IIb mouse had higher Pi concentrations in the bronchoalveolar fluid with microcrystals, invasion of macrophages and signs of inflammation and fibrosis [86]. Microcrystals were resolved by EDTA bronchoalveolar lavage or by placing mice on a low Pi diet for 4 weeks. The relevance of these experimental therapies remains to be tested in patients.

Dysregulation of NaPi-IIb in disease

Inflammatory bowel disease

Patients with inflammatory bowel disease are at risk to develop bone disease with low bone mineral density. Malabsorption of vitamin D_3, calcium and phosphate can contribute to the risk. Inflammation has been shown to downregulate NaPi-IIb expression in a TNF-dependent manner [12]. In addition, TNF may also downregulate bone PHEX expression and thereby indirectly increase FGF23 levels which woukld reduce 1,25-$(OH)_2$ Vitamin D_3 dependent stimulation of NaPi-IIb expression [94].

Chronic kidney disease

In patients with chronic kidney disease, mineral metabolism is severely disturbed. The profile of hormones regulating mineral metabolism is altered. FGF23 rises whereas a-klotho 1,25-$(OH)_2$-vitamin D_3 fall early during the development of CKD [36,77]. Later

PTH is increased and eventually plasma phosphate elevated. The loss of functional nephrons progressively reduces the renal ability to excrete phosphate. Nevertheless, plasma phosphate remains within the normal range until CKD progresses to end-stage renal disease (ESRD, stages 4 and 5), as remaining healthy nephrons compensate [8].

Hyperphosphatemia is a major risk factor for all-cause mortality in CKD patients [49,6] and. cardiovascular disease is the leading cause of mortality in this vulnerable population [9,29]. Thus, targeting hyperphosphatemia is of outmost importance in patients with CKD. Current strategies addressing hyperphosphatemia include restricted dietary phosphate intake together with phosphate binders [82]. More recently, pharmaceutical strategies were described targeting NaPi-IIb mediated intestinal phosphate absorption [26].

In uremic mice, the application of a phosphate bolus increased plasma phosphate and FGF23 despite the presence of a phosphate binder. This increase was blunted in mice with a conditional whole body deletion of NaPi-IIb also receiving a phosphate binder [87]. These data suggested that the combined reduction of freely absorbable phosphate with the inhibition of NaPi-IIb (i.e. the reduction of the paracellular pathway for phosphate and the inhibition of transcellular Pi transport) could be an effective strategy to lower phosphate loads in patients with reduced kidney function.

Consistent with the lack of evidence for a systemic alteration of phosphate homeostasis, the direct inhibition of NaPi-IIb with a specific inhibitor has failed in a phase I and II study having no impact on plasma phosphate and FGF23 levels [61]. Unfortunately, no trial has been reported yet combining a NaPi-IIb specific inhibitor with phosphate binders.

Nicotinamide and niacin have been reported to reduce NaPi-IIb expression and to lower plasma phosphate levels both in experimental animal studies and in small trials with patients with CKD [22,44,91]. The exact mechanism how these compounds reduce intestinal phosphate absorption is not fully clear. A common metabolite of both

substances is NAD^+ which has been shown to directly (and maybe also indirectly) inhibit renal and intestinal Pi transport [46]. Very recent evidence suggests that NAD^+ mediates at least in part the circadian regulation of renal and intestinal Pi transporters [71,92]. On-going clinical trials test the efficacy of nicotinamide in combination with conventional phosphate binders in the NOPHOS (EU Clinical Trials Register 2013-000488-95) and COMBINE (ClinicalTrials.gov Identifier: NCT02258074) trials.

Similarly, tenapanor, an inhibitor of the Na^+/H^+ exchanger isoform 3 (NHE3) reduces intestinal Pi absorption [58]. Initially, it had been speculated that tenapanor may also modulate NaPi-IIb activity and/or expression but recent data demonstrated that the substance acts on paracellular Pi fluxes without affecting active transcellular Pi transport [52].

NaPi-IIb and cancer

Studies dating from the 1980s have suggested that NaPi-IIb can be used as a marker for specific tumors including ovarian and lung cancer, although the identity of NaPi-IIb as the marker was initially unknown (reviewed in [59]). A monoclonal antibody was developed to identify epithelial tumors through binding to an antigen named MX35, which on further characterization was found to be NaPi-IIb [63]. In the tumors expressing NaPi-IIb, the protein has been identified as wild type; however, a recent phenomenon whereby *SLC34A2* undergoes molecular re-arrangement with ROS-1, a tyrosine kinase receptor, to create a constitutively active tyrosine kinase that increases oncogenicity has been described [45,16]. Furthermore, there is some evidence that high expression of NaPi-IIb may confer resistance to cancer chemotherapy and may increase metastatic potential [59].

Summary and outlook

Phosphate is critical for many cellular and organ functions. Its absorption and excretion as well as its (re)distribution in the body depend at least in part on Na^+-

dependent phosphate transporters of the SLC34 gene family. It is thus not surprising that mutations in all three members of this family can cause distinct pathologies in humans. The high frequency of monoallelic mutations in SLC34A1 may have relevance for the susceptibility of adults to form kidney stones. The role of SLC34A1 in CKD risk remains to be explored as well as the role of SLC34A2 in cancer. If substantiated, NaPi-IIa and NaPi-IIb may also become targets for pharmacological interventions in these diseases. Attempts to target NaPi-IIb in controlling hyperphosphatemia in patients with CKD have not been successful to date but may need to be combined with other approaches to lower bioavailable intestinal phosphate concentrations to be effective.

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Figure legends

Table 1

Summary of diseases that have been proven to be caused by alterations in the function of SLC34A1 or SLC34A2 and diseases with associations with the two genes but where the causative relationship has not been well established yet.

Figure 1

Model explaining how reduced function of SLC34A1 (due to loss-of-function mutations or dysregulation) can cause dysregulation of hormones regulating mineral homeostasis and supports the development of nephrocalcinosis and -lithiasis. Red arrows and boxes indicate hormones or processes downregulated, green arrows and boxes indicate hormones or processes upregulated. For details, please see text. $sHPO_4^{2-}$ (serum phosphate), $uHPO_4^{2-}$ (urine phosphate), uCa^{2+} (urine calcium), sCa^{2+} (serum calcium)

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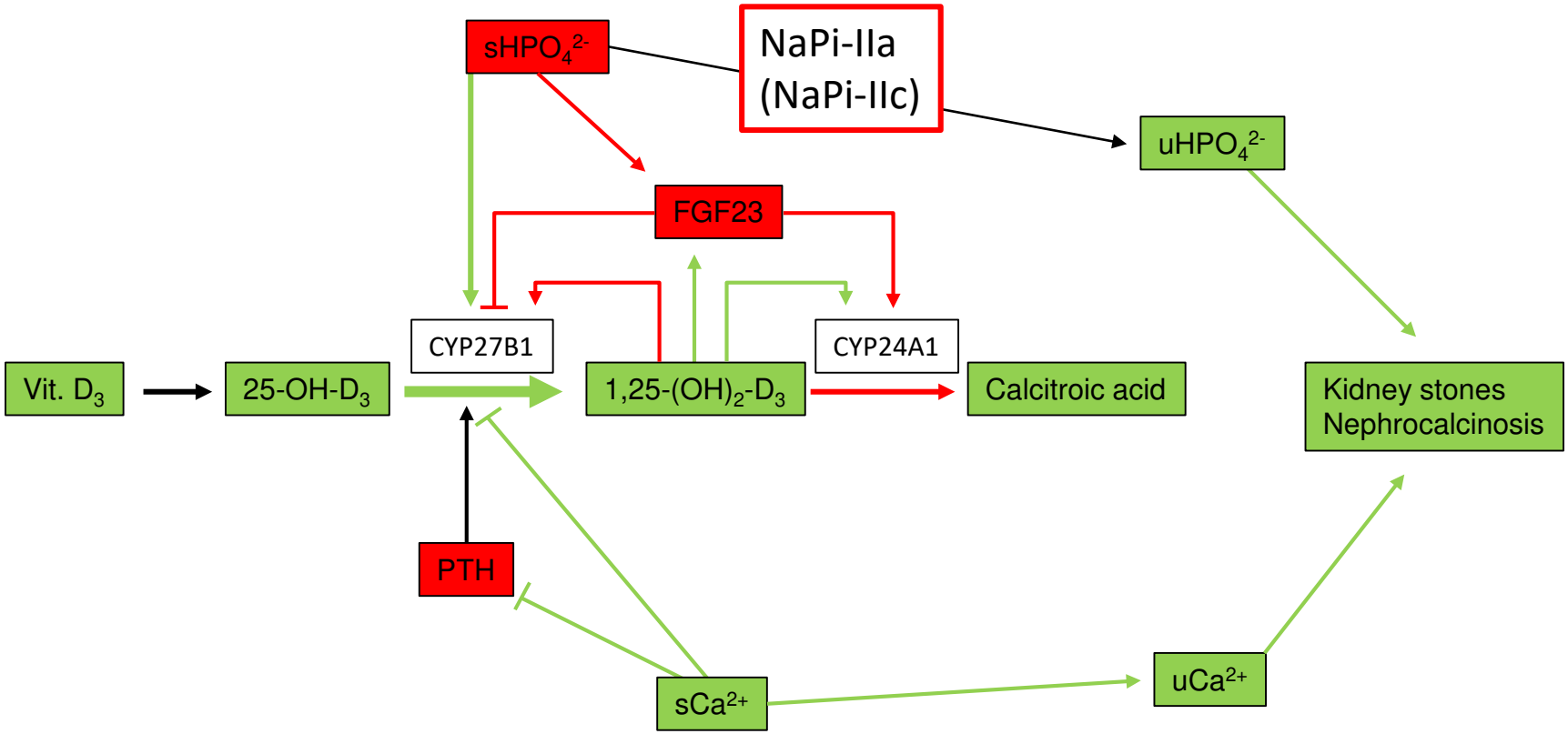
Table 1: SLC34A1 and SLC34A2 Mutations and Clinical Disease Associations

Transporter	Identified Disease Associations	Implicated Clinical Associations
SLC34A1	Osteopenia Nephrolithiasis Nephrocalcinosis Idiopathic Infantile Hypercalcemia	Chronic Kidney Disease Salt Sensitive Hypertension Serum Phosphate Level Serum PTH Level Serum FGF23 Level
SLC34A2	Pulmonary Alveolar Microlithiasis	Cancer Metastasis and Chemotherapy Resistance


sHPO4 2-
NaPi-IIa
(NaPi-IIc)
uHPO4 2-
FGF23
CYP27B1
CYP24A1
Vit. D3
25-OH-D3
1,25-(OH)2-D3
Calcitroic acid
Kidney stones
Nephrocalcinosis
PTH
sCa2+
uCa2+